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APPLICATION NUMBER: 60/053,535

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## PRIORITY DOCUMENT

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07/23/97

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (b)(2).

|  |                  |                                 |   |  |        |          |  |
|--|------------------|---------------------------------|---|--|--------|----------|--|
| CASE NUMBER  |                  |                                 |   |  |        | 20002PV2 |  |
| INVENTOR(S)  |                  |                                 |   |  |        |          |  |
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| <input type="checkbox"/> Additional inventors are being named on the __ separately numbered sheets attached hereto                   |                  |                                 |   |  |        |          |  |
| TITLE OF THE INVENTION (280 characters max)  |                  |                                 |   |  |        |          |  |
| ORAL METHOD FOR TREATING OR PREVENTING ABNORMAL BONE RESORPTION  |                  |                                 |   |  |        |          |  |
| CORRESPONDENCE ADDRESS   |                  |                                 |   |  |        |          |  |
| Merck & Co., Inc.<br>Patent Department - RY60-30<br>P.O. Box 2000<br>Rahway  |                  |                                 |   |  |        |          |  |
| STATE  | New Jersey       | ZIP CODE                        | 07065   | COUNTRY  | U.S.A. |          |  |
| ENCLOSED APPLICATION PARTS (check all that apply)  |                  |                                 |   |  |        |          |  |
| <input checked="" type="checkbox"/> Specification  | Number of Pages  | 39                              | <input type="checkbox"/> Small Entity Statement |  |        |          |  |
| <input checked="" type="checkbox"/> Drawing(s)   | Number of Sheets | 4                               | <input type="checkbox"/> Other (specify)        |  |        |          |  |
| METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)   |                  |                                 |   |  |        |          |  |
| <input type="checkbox"/> A check or money order is enclosed to cover the filing fees   |                  |                                 |   | FILING FEE AMOUNT (\$)   |        | \$150.00 |  |
| <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number: |                  |                                 |   | 13-2755  |        |          |  |

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,  
SIGNATURE *[Signature]*

Date 7/23/97

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TITLE OF THE INVENTION  
ORAL METHOD FOR TREATING OR PREVENTING ABNORMAL  
BONE RESORPTION

5 FIELD OF THE INVENTION

The present invention relates to oral methods for treating or preventing abnormal bone resorption in a mammal while minimizing the occurrence of adverse gastrointestinal effects. These methods comprise orally administering a pharmaceutically effective amount of a  
10 bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The method is continued until the desired therapeutic effect is achieved. The present invention also relates to pharmaceutical  
15 compositions and kits useful in these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include,  
20 but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and  
25 microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

30 Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone

disorders caused by or associated with abnormal bone resorption. See H. Fleisch, *Bisphosphonates In Bone Disease, From The Laboratory To The Patient*, 2nd Edition, Parthenon Publishing (1995), which is incorporated by reference herein in its entirety.

- 5       At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other bisphosphonates such as risedronate, tiludronate, ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An  
10   older bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization. See Boyce, B. F., Fogelman, I., Ralston, S. et al.  
15   (1984) *Lancet* 1(8381), pp. 821-824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) *Br. Med. J.* 292, pp. 1227-1229 (1986), both of which are incorporated by reference herein in their entirety.

- Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract. See B.J. Gertz et al., *Clinical  
20   Pharmacology of Alendronate Sodium, Osteoporosis Int.*, Suppl. 3: S13-16 (1993) and B.J. Gertz et al., *Studies of the oral bioavailability of alendronate, Clinical Pharmacology & Therapeutics*, vol. 58, number 3, pp. 288-298 (September 1995). Intravenous administration has been used to overcome this bioavailability problem. However, intravenous  
25   administration is costly and inconvenient, especially when the patient must be given an intravenous infusion lasting several hours on repeated occasions. If oral administration of the bisphosphonate is desired, relatively high doses must be administered to compensate for the low bioavailability from the gastrointestinal tract. To offset this  
30   bioavailability problem, it is generally recommended that the patient take the bisphosphonate on an empty stomach and fast for at least 30 minutes afterwards. However, many patients find the need for such fasting on a daily basis to be inconvenient. Moreover, oral administration has been associated with adverse gastrointestinal effects,

especially those relating to the esophagus. See Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate has been associated with esophageal ulcers. See E.G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320-322 (1994). Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. See P.C. De Groen, et al., *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016-1021, 1058-1059, and 1069-1070 (October 3, 1996). The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. See C.H. Chestnut et al., *Alendronate Treatment of the Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144-152, (August 1995). Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily dosing has the disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be

burdensome. These factors can therefore interfere with patient compliance, and in severe cases even require cessation of treatment.

Cyclic treatment regimens were developed because some bisphosphonates, such as etidronate, when given daily for more than several days, have the disadvantage of actually causing a decline in bone mineralization, i.e. osteomalacia. U.S. Patent No. 4,761,406, to Flora et al, issued August 2, 1988, describes a cyclic regimen developed in an attempt to minimize the decline in bone mineralization while still providing a therapeutic anti-resorptive effect. Generally, cyclic regimens are characterized as being intermittent, as opposed to continuous treatment regimens, and have both treatment periods during which the bisphosphonate is administered and nontreatment periods to permit the systemic level of the bisphosphonate to return to baseline. However, the cyclic regimens, relative to continuous dosing, appear to result in a decreased therapeutic antiresorptive efficacy. Data on risedronate suggests that cyclic dosing is actually less effective than continuous daily dosing for maximizing antiresorptive bone effects. See L. Mortensen, et al., *Prevention Of Early Postmenopausal Bone Loss By Risedronate*, *Journal of Bone and Mineral Research*, vol. 10, supp. 1, p. s140 (1995). Furthermore, these cyclic regimens do not eliminate or minimize adverse gastrointestinal effects, because such regimens typically utilize periods of multiple daily dosing. Also, the cyclic regimens are cumbersome to administer and have the disadvantage of low patient compliance, and consequently compromised therapeutic efficacy. U.S. Patent No. 5,366,965, to Strein, issued November 22, 1994, attempts to address the problem of adverse gastrointestinal effects by administering a polyphosphonate compound, either orally, subcutaneously, or intravenously, according to an intermittent dosing schedule having both a bone resorption inhibition period and a nontreatment rest period. However, the regimen has the disadvantage of not being continuous and regular, and requires nontreatment periods ranging from 20 to 120 days. PCT Application No. WO 95/30421, to Goodship et al, published November 16, 1995, discloses methods for preventing prosthetic loosening and migration using various

bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages. It is seen from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects often associated with daily or cyclic dosing regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects would be expected to increase as a function of increasing bisphosphonate dosage.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better therapeutic efficacy.

It is an object of the present invention to provide oral methods for treating abnormal bone resorption and the conditions associated therewith.

It is another object of the present invention to provide oral methods for preventing abnormal bone resorption and the conditions associated therewith.

5 It is another object of the present invention to provide such methods comprising a continuous dosing schedule having a dosing interval selected from the group consisting of weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

10 It is another object of the present invention to provide such methods wherein the continuous dosing schedule is maintained until the desired therapeutic effect is achieved.

It is another object of the present invention to treat or prevent abnormal bone resorption in an osteoporotic mammal, preferably an osteoporotic human.

15 It is another object of the present invention to provide pharmaceutical compositions and kits useful in the methods herein.

These and other objects will become readily apparent from the detailed description which follows.

#### SUMMARY OF THE INVENTION

20 The present invention relates to an oral method for treating abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage  
25 according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing, wherein said continuous schedule is maintained until the desired therapeutic effect is achieved for said mammal.

30 In other embodiments, the present invention relates to an oral method for preventing abnormal bone resorption in a mammal.

In other embodiments, the present invention relates to an oral method for treating or preventing abnormal bone resorption in a human.

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In other embodiments, the present invention relates to an oral method for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to an oral method for treating or preventing abnormal bone resorption in a human  
5 in need of such treatment comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a  
10 pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated,  
15 are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

#### BRIEF DESCRIPTION OF THE FIGURES

20 FIG. 1 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with five separate dosages of 50 mL of simulated gastric juice on five consecutive days.

25 FIG. 2 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated gastric juice on five consecutive days.

30 FIG. 3 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

FIG. 4 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 7 days after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

5

#### DESCRIPTION OF THE INVENTION

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The present invention relates to an oral method for treating or preventing abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects. The methods of the present invention comprise orally administering to a mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage, wherein said dosage is administered according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. Typically, the continuous dosing schedule is maintained until the desired therapeutic effect is achieved for the mammal. The present invention utilizes higher unit dosages of the bisphosphonate at each dosing point than has heretofore been typically administered, yet because of the dosing schedule chosen, adverse gastrointestinal effects are minimized. Moreover, the method is more convenient because the disadvantages associated with daily dosing are minimized.

25 The term "pharmaceutically effective amount", as used herein, means that amount of the bisphosphonate compound, that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the bisphosphonate is a bone resorption inhibiting amount.

30 The term "minimize the occurrence of adverse gastrointestinal effects", as used herein, means preventing, decreasing, or lessening the occurrence of unwanted side effects in the gastrointestinal tract, i.e. the esophagus, stomach, intestines, and rectum, particularly the esophagus. Nonlimiting adverse gastrointestinal effects include, but are not limited

to esophagitis, esophageal ulcers, esophageal irritation, esophageal perforation, abdominal pain, gastric duodenal ulcers, and constipation.

5 The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

10 The term "bone resorption inhibiting", as used herein, means preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

15 The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the once-weekly, twice-weekly, biweekly, or twice-monthly dosing interval is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

20 The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition being treated is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is  
25 continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously  
30 administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the

remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably from about 6 months to about 10 years, and most preferably from about 1 year to about 10 years.

5

#### Methods of the Present Invention

The present invention comprises methods for treating abnormal bone resorption in mammals. The present invention also comprises methods for preventing abnormal bone resorption in mammals. In  
10 preferred embodiments of the present invention, the mammal is a human.

The methods of the present invention do not have the disadvantages of current methods of treatment which can cause adverse gastrointestinal effects or which require cumbersome, irregular, or  
15 complicated dosing regimens.

The present invention comprises a continuous dosing schedule whereby a unit dosage of the bisphosphonate is regularly administered according to a dosing interval selected from the group consisting of  
20 once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

By once-weekly dosing is meant that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven day period, preferably on the same day of each week. In the once-weekly dosing regimen, the unit dosage is generally administered about  
25 every seven days. A nonlimiting example of a once-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the once-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on  
30 two consecutive days falling within two different weekly periods.

By twice-weekly dosing is meant that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on the same two days of each weekly period. In the twice-weekly dosing regimen, each unit dosage is

generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or on two or more consecutive days falling within two different consecutive weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period or on two or more consecutive days within two different consecutive monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens

have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen (because there are twelve  
5 calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

The methods and compositions of the present invention are useful for both treating and preventing abnormal bone resorption and  
10 conditions associated therewith.

Conditions associated with abnormal bone resorption include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means  
15 bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is often associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein  
20 estrogen production has been greatly diminished. However, osteoporosis can also be steroid-induced and has been observed in males due to age. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis, it can be induced by secondary causes, e.g., glucocorticoid therapy, or it can come about with no identifiable cause, i.e. idiopathic  
25 osteoporosis. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease, with bone fractures, and with periprosthetic osteolysis (in other words  
30 where bone resorption has occurred in proximity to a prosthetic implant).

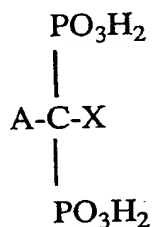
Generalized or localized bone loss can occur from disuse, which is often a problem for those confined to a bed or a wheelchair, or for those who have an immobilized limb set in a cast or in traction.

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; osteomalacia; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its entirety.

#### Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



20

wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH<sub>2</sub>, SH, phenyl, C1-C30 alkyl, C1-C30 substituted alkyl, C1-C10 alkyl or dialkyl substituted NH<sub>2</sub>, C1-C10 alkoxy, C1-C10 alkyl or phenyl substituted thio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those

30

selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH<sub>2</sub>, C1-C10 alkyl or dialkyl substituted NH<sub>2</sub>, OH, SH, and C1-C10 alkoxy,

- 5 In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, 10 quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, halogen, and C1-C10 alkyl or phenyl substituted thio.

- 15 More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C1-C30 alkyl, C1-C30 substituted alkyl, Cl, and chlorophenylthio.

- 20 Most preferred is when A is OH and X is 4-aminobutyl, i.e. alendronate.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1-C30-alkyl- 25 substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

- 30 "Pharmaceutically acceptable" as used herein means that the salts and derivatives of the bisphosphonates have the same general pharmacological properties as the free acid form from which they are derived and are acceptable from a toxicity viewpoint.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents



of the present invention are meant to also encompass diphosphonates, biposphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit  
5 the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70  
10 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

15 Nonlimiting examples of bisphosphonates useful herein include the following :

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

20 Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Patents 4,922,007, to Kieczkowski et al., issued May 1, 1990, and 5,019,651, to Kieczkowski, issued May 28, 1991, both of which are  
25 incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

30 1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidiny)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate sodium trihydrate.

#### Pharmaceutical Compositions

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Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Patent No. 5,358,941, to Bechard et al, issued October 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-methacrylamide, and the like.

The precise dosage of the bisphosphate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the

disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician.

Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 µg/kg body weight and preferably about 10 to about 2000 µg/kg of body weight.

For oral compositions comprising alendronate, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable derivatives thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 70 mg of the

alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

- Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

- In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L.J. Hixson, et al., *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease*, Arch. Intern. Med., vol. 152, pp. 726-732 (April 1992), which is incorporated by reference herein in its entirety. It has been found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphosphonate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

- Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

Treatment Kits

In further embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium or dietary supplements, either in a form similar to or distinct from the bisphosphonate dosages, can be included to provide a kit in which a dosage is taken every day. In those embodiments including a histamine H2 receptor and/or proton pump inhibitor, these agents can be included as part of the kit.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE 1

Esophageal Irritation Potential

The esophageal irritation potential of alendronate monosodium trihydrate is evaluated using a dog model. The experiments compare the irritation potential of a single high concentration alendronate dosage

versus the irritation potential of a low concentration dosage administered for five consecutive days.

The following solutions are prepared :

- (1) simulated gastric juice (pH about 2), i.e. the control solution.
- 5 (2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

10 The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of  
15 the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a  
20 rubber catheter. The following treatment experiments are run:

- Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed about 24 hours after the last dose is administered.
- 25 Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed about 24 hours after the last dose is administered.
- 30 Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

5           Group 4: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 7 days after the dose is administered.

10           The esophagus from each sacrificed animal is removed and prepared for histopathology using standard techniques by embedding the tissue in paraffin, staining with hematoxylin and eosin. The sections are examined microscopically. The histopathology results are summarized in Table 1.

15           For the Group 1 animals (control group), the photomicrographs show that the esophagus is normal with an intact epithelium and absence of inflammatory cells in the submucosa. FIG. 1 is a representative photomicrograph from a Group 1 animal.

20           For the Group 2 animals, the photomicrographs show that the esophagus exhibits deep ulceration of the epithelial surface and marked submucosal inflammation and vacuolation. FIG. 2 is a representative photomicrograph from a Group 2 animal.

25           For the Group 3 animals, the photomicrographs show that the esophagus has an intact epithelial surface with little submucosal inflammation and vacuolation. FIG. 3 is a representative photomicrograph from a Group 3 animal.

30           For the Group 4 animals, the photomicrographs show that the esophagus has an intact epithelium with either minimal inflammation (two of the five animals) or no inflammation (three of the five animals) and no vacuolation. FIG. 4 is a representative photomicrograph from a Group 4 animal exhibiting minimal inflammation.

          These experiments demonstrate that considerably less esophageal irritation is observed from the administration of a single high concentration dosage of alendronate (Groups 3 and 4) versus administration of low concentration dosages on consecutive days (Group 2).



Table 1.

| Esophageal Irritation Potential Studies |                      |                        |                                  |   |
|---|----------------------|------------------------|----------------------------------|---|
| Group                                   | Alendronate<br>mg/mL | Dosing<br>Schedule     | Sacrifice<br>Time                | Histo-pathology   |
| 1<br>(n=4)                              | 0                    | 1X daily<br>for 5 days | 24 hours<br>after last<br>dosing | Normal. Intact<br>epithelium and<br>absence of<br>inflammatory cells<br>in the submucosa.   |
| 2<br>(n=4)                              | 0.20                 | 1X daily<br>for 5 days | 24 hours<br>after last<br>dosing | Deep ulceration of<br>epithelial surface.<br>Marked submucosal<br>inflammation and<br>vacuolation.  |
| 3<br>(n=5)                              | 0.80                 | 1X daily<br>for 1 day  | 24 hours<br>after<br>dosing      | Intact epithelial<br>surface with little<br>submucosal<br>inflammation and<br>vacuolation.  |
| 4<br>(n=5)                              | 0.80                 | 1X daily<br>for 1 day  | 7 days<br>after<br>dosing        | Intact epithelium<br>with either minimal<br>inflammation (2 of<br>5 animals) or no<br>inflammation (3 of<br>5 animals) and no<br>vacuolation. |

EXAMPLE 2

5

Once-weekly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

10 Prevention of osteoporosis.

Alendronate tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient once-weekly, i.e. preferably about once every seven days (for example, every Sunday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

20 EXAMPLE 3

Twice-weekly dosing regimen.

Treatment of osteoporosis.

25 Alendronate tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient twice-weekly, preferably about once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient twice-weekly, preferably about  
5 once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient  
10 acceptance and compliance.

EXAMPLE 4

Biweekly dosing regimen

15

Treatment of osteoporosis.

Alendronate tablets containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient biweekly, i.e. preferably about  
20 once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

25

Prevention of osteoporosis.

Alendronate tablets containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient biweekly, i.e. preferably about  
30 once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

EXAMPLE 5

5 Twice-monthly dosing regimen.

Treatment of osteoporosis.

Alendronate tablets containing about 140 mg of alendronate, on an  
alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet  
10 is orally administered to a human twice-monthly, i.e. preferably about  
once every fourteen to sixteen days (for example, on about the first and  
fifteenth of each month), for a period of at least one year. This method  
of administration is useful and convenient for treating osteoporosis and  
for minimizing adverse gastrointestinal effects, particularly adverse  
15 esophageal effects. This method is also useful for improving patient  
acceptance and compliance.

Prevention of osteoporosis.

Alendronate tablets containing about 70 mg of alendronate, on an  
20 alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet  
is orally administered to a human patient biweekly, i.e. preferably once  
every fourteen to sixteen days (for example, on about the first and  
fifteenth of each month), for a period of at least one year. This method  
of administration is useful and convenient for preventing osteoporosis  
25 and for minimizing adverse gastrointestinal effects, particularly adverse  
esophageal effects. This method is also useful for improving patient  
acceptance and compliance.

EXAMPLE 6

30

In further embodiments, alendronate tablets are orally dosed, at the  
desired dosage, according to the dosing schedules of EXAMPLES 2-5,  
for treating or preventing other disorders associated with abnormal  
bone resorption.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

EXAMPLE 7

10 Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

|    |                                   |                   |                         |
|----|-----------------------------------|-------------------|-------------------------|
| 20 | <u>Ingredient</u>                 | <u>Per Tablet</u> | <u>Per 4000 Tablets</u> |
|    | Alendronate Monosodium Trihydrate | 45.68 mg          | 182.72 g                |
| 25 | Anhydrous Lactose, NF             | 71.32 mg          | 285.28 g                |
|    | Microcrystalline Cellulose, NF    | 80.0 mg           | 320.0 g                 |
|    | Magnesium Stearate, NF            | 1.0 mg            | 4.0 g                   |
| 30 | Croscarmellose Sodium, NF         | 2.0 mg            | 8.0 g                   |

The resulting tablets are useful for administration in accordance with the methods of the present invention for treating or preventing bone resorption.

- Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active basis are prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared:
- 5 e.g., cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

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WHAT IS CLAIMED IS:

1. An oral method for treating abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
2. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
3. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
4. A method according to claim 3 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.
5. A method according to claim 4 wherein said mammal is a human.
6. A method according to claim 5 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.
7. A method according to claim 5 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

8. A method according to claim 5 wherein said dosing interval is biweekly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

5

9. A method according to claim 5 wherein said dosing interval is twice-monthly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

10

10. A method according to any of claims 1-9 wherein said mammal is an osteoporotic mammal.

15

11. An oral method for treating osteoporosis in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

20

25

12. An oral method for preventing abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

30

13. A method according to claim 12 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.



14. A method according to claim 12 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

5

15. A method according to claim 14 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

16. A method according to claim 15 wherein said mammal is a human.

10

17. A method according to claim 16 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

15

18. A method according to claim 16 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

20

19. A method according to claim 16 wherein said dosing interval is biweekly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

25

20. A method according to claim 16 wherein said dosing interval is twice-monthly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

30

21. A method according to any of claims 12-20 wherein said mammal is an osteoporotic mammal.

22. An oral method for preventing osteoporosis in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to

said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

5

23. An oral method for treating abnormal bone resorption in a human in need of such treatment comprising orally administering to said human a unit dosage of a bisphosphonate, said unit dosage comprising from about 17.5 mg to about 140 mg, on an alendronic acid basis, of a  
10 bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis.

24. A method according to claim 23 wherein said unit dosage  
15 comprises about 35 mg of the bisphosphonate.

25. A method according to claim 23 wherein said unit dosage comprises about 70 mg of the bisphosphonate.

20 26. A method according to claim 25 wherein said unit dosage is administered once-weekly.

27. A method according to claim 23 wherein said unit dosage  
25 comprises about 140 mg of the bisphosphonate.

28. An oral method for preventing abnormal bone resorption in a human in need of such treatment comprising orally administering to said human a unit dosage of a bisphosphonate, said unit dosage comprising from about 8.75 mg to about 70 mg, on an alendronic acid  
30 basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis.

29. A method according to claim 28 wherein said unit dosage comprises about 17.5 mg of the bisphosphonate.

5 30. A method according to claim 28 wherein said unit dosage comprises about 35 mg of the bisphosphonate.

31. A method according to claim 30 wherein said unit dosage is administered once-weekly.

10 32. A method according to claim 28 wherein said unit dosage comprises about 70 mg of the bisphosphonate.

33. An oral method for treating abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of  
15 adverse gastrointestinal effects, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a  
20 continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, twice-monthly dosing.

34. A method according to claim 33 wherein said histamine H2 blocker or said proton pump inhibitor is administered from about 30  
25 minutes to about 24 hours prior to the administration of said bisphosphonate.

35. An oral method for preventing abnormal bone resorption in a mammal human in need of such treatment, while minimizing the  
30 occurrence of adverse gastrointestinal effects, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group

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consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, twice-monthly dosing.

36. A method according to claim 35 wherein said histamine H2  
5 blocker or said proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of said bisphosphonate.

37. A pharmaceutical composition comprising about 70 mg, on  
10 an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

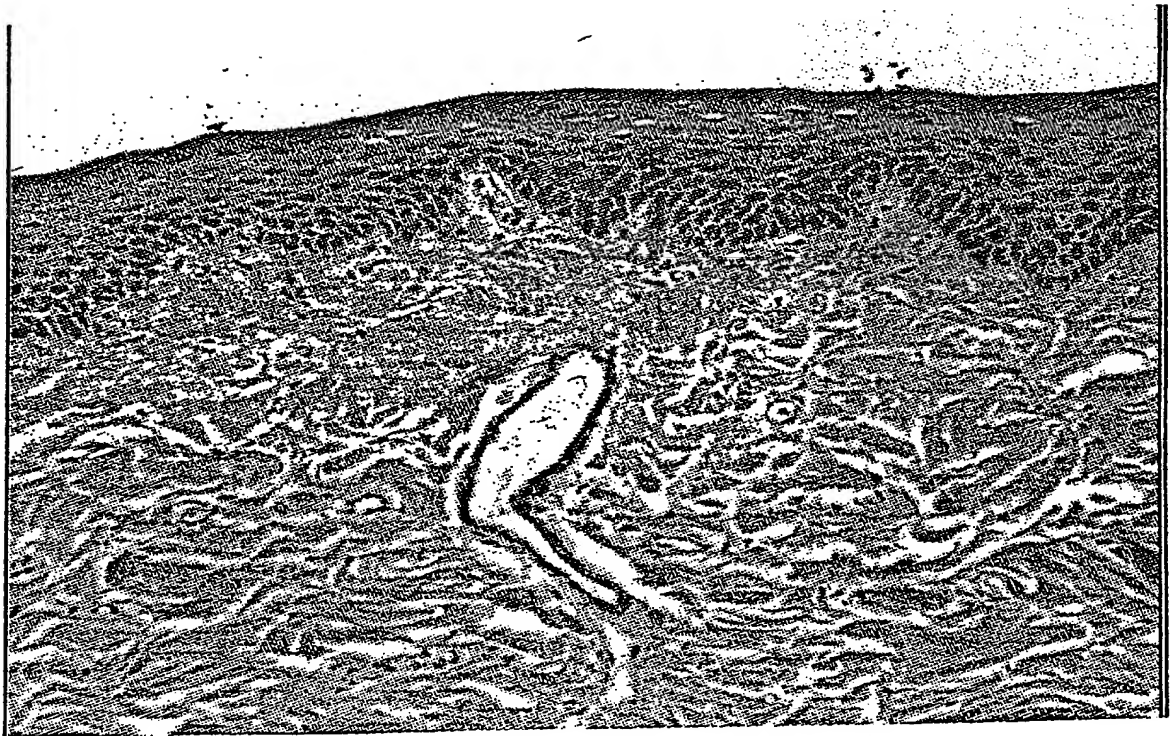
38. A pharmaceutical composition comprising about 140 mg,  
15 on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

39. A kit for orally treating abnormal bone resorption in a  
20 mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing,  
25 twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

40. A kit for orally preventing abnormal bone resorption in a  
mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said kit comprising at least one  
30 pharmaceutically effective unit dosage of a bisphosphonate for oral administration according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

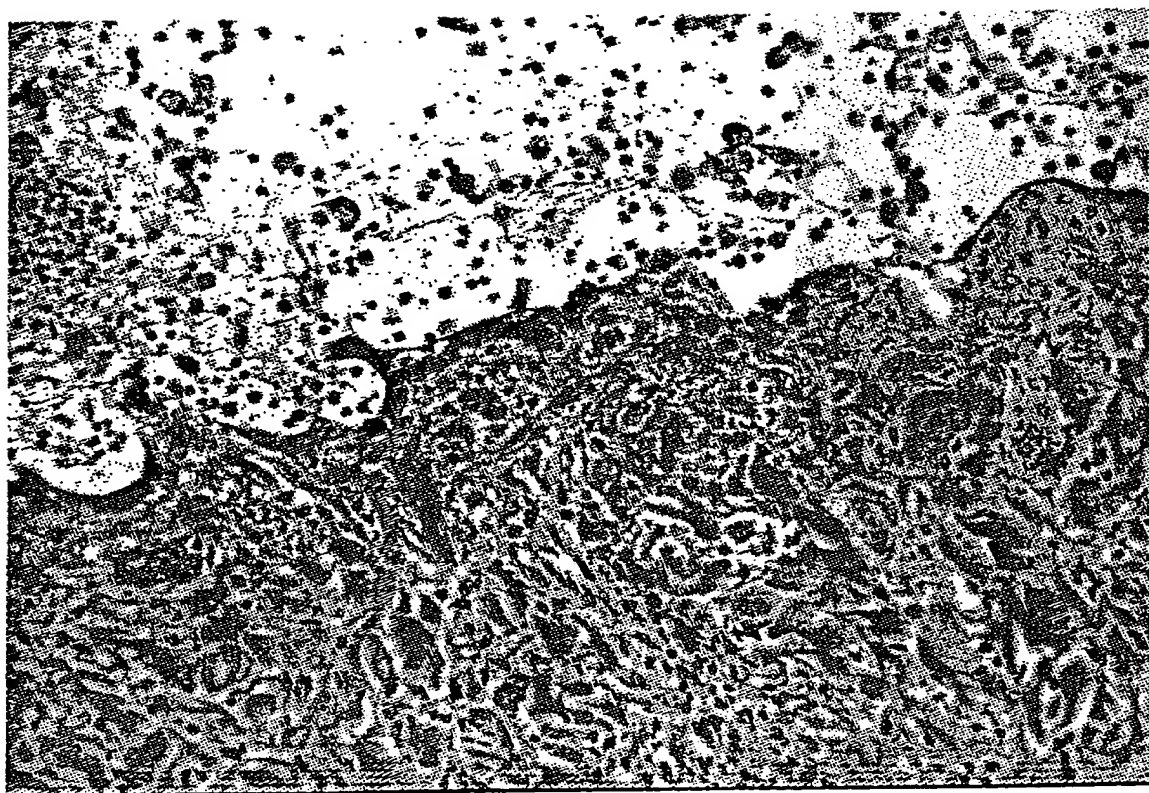
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FIG. 1



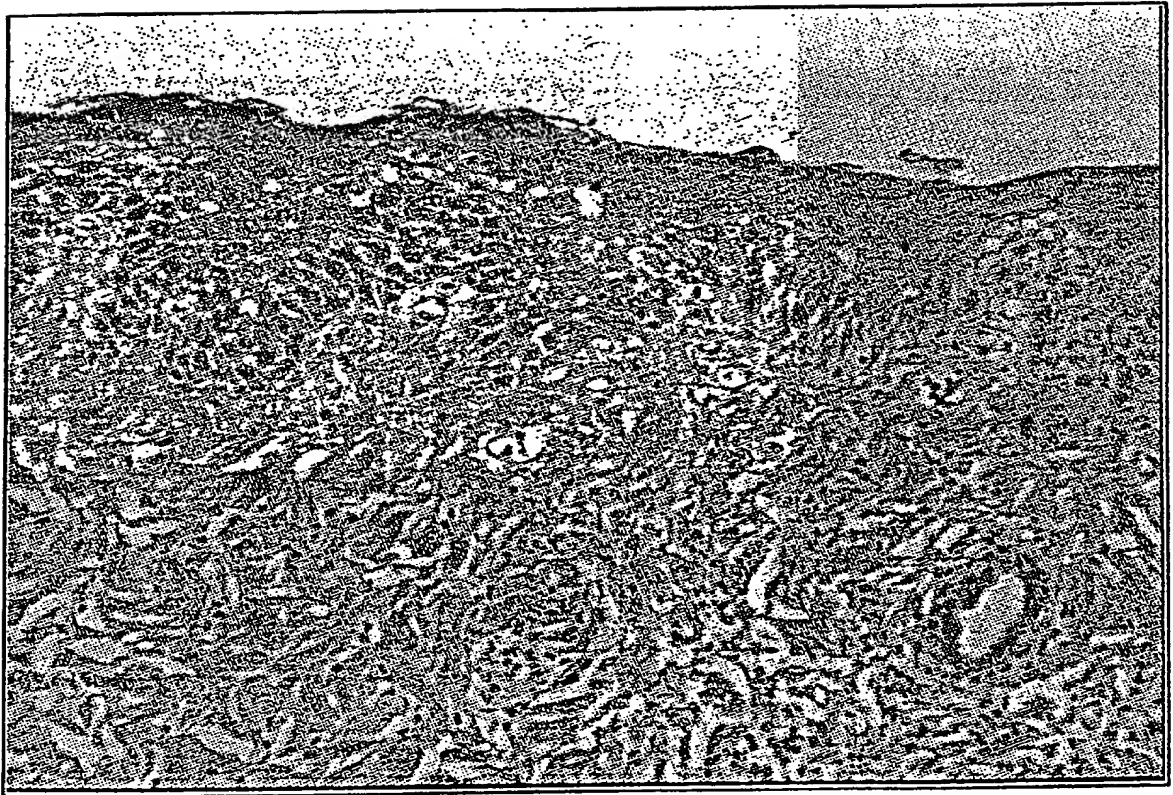
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FIG. 2



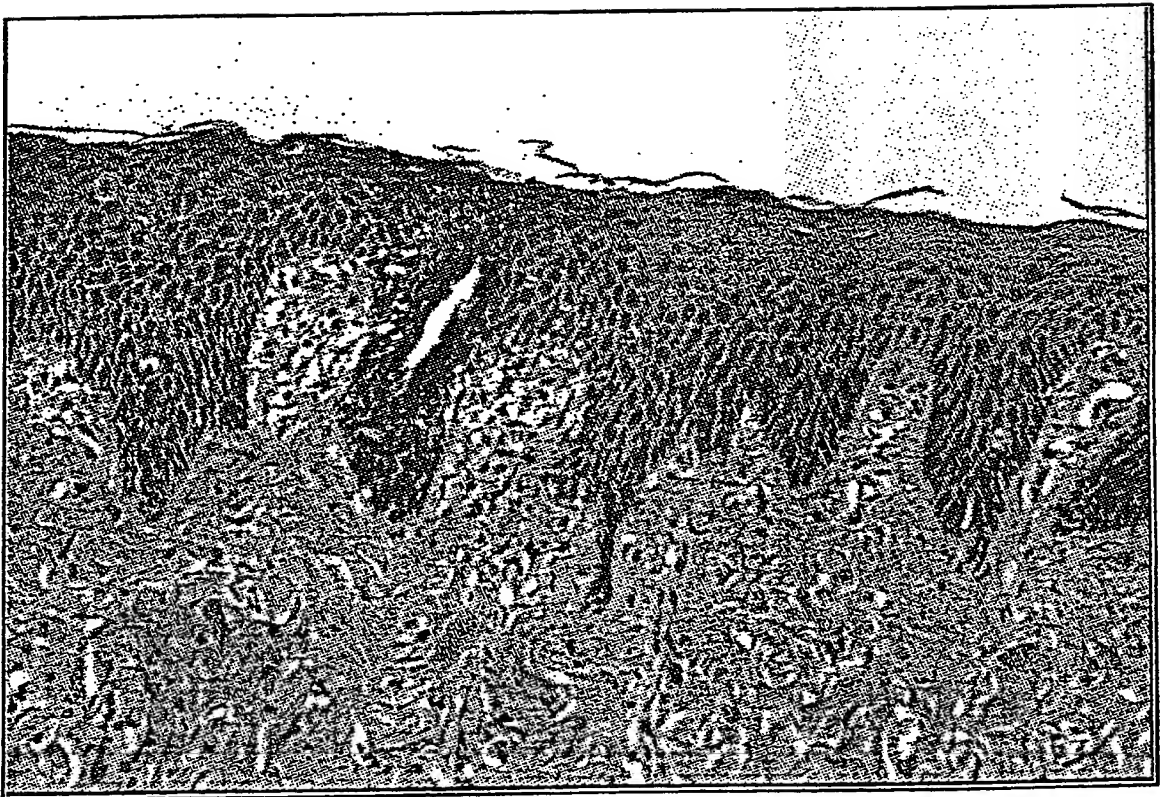
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FIG. 3



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FIG. 4



20002PV2



TITLE OF THE INVENTION  
ORAL METHOD FOR TREATING OR PREVENTING ABNORMAL  
BONE RESORPTION

5

ABSTRACT OF THE INVENTION

Disclosed are methods for treating or preventing abnormal bone  
resorption in mammals while minimizing the occurrence of adverse  
gastrointestinal effects. Also disclosed are pharmaceutical compositions  
and kits for carrying out the therapeutic methods.

10

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